by ALAN L. BERKOWITZ, MD

Dr. Berkowitz is from the Behavioral Medicine Center, Pomerado Hospital, San Diego, California.

Ziprasidone Therapy in Elderly Patients with Psychotic Mood Disorders and Parkinson's Disease

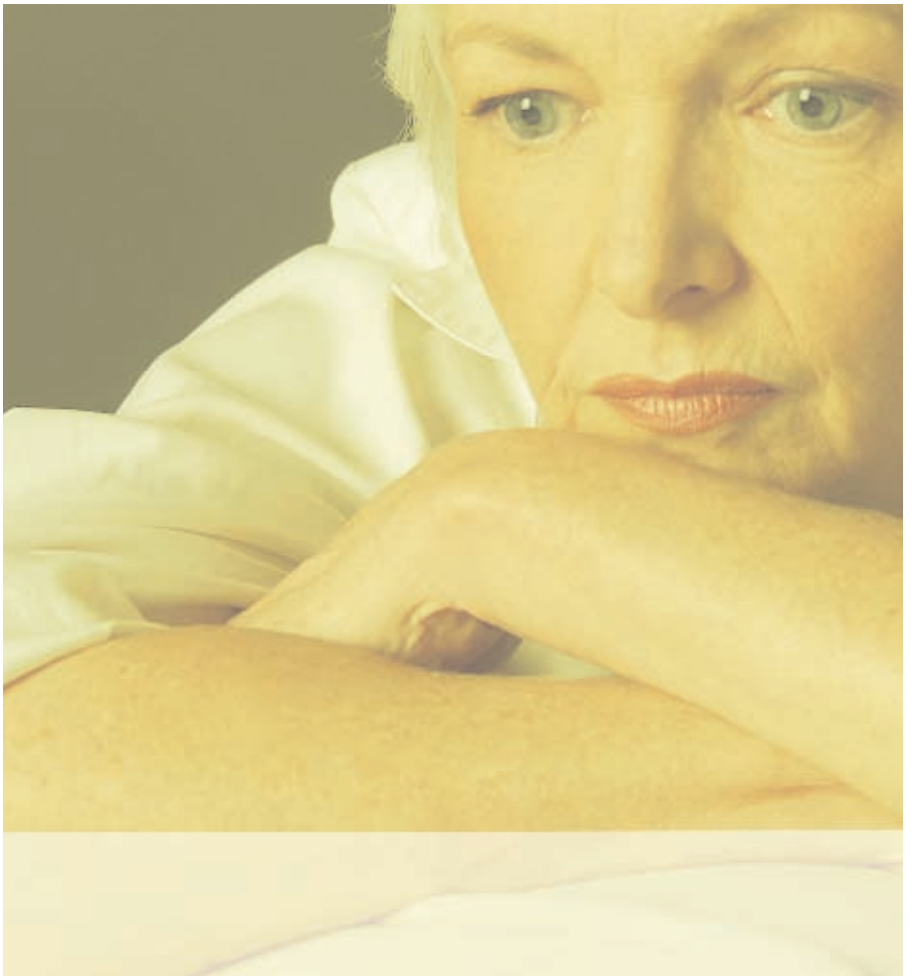
ABSTRACT

Objective: To illustrate and discuss issues relevant to treatment of four elderly psychotic patients with multiple comorbidities, including a history of mood disorder and some level of movement disorder.

Participants: Four patients diagnosed with a major mood disorder and comorbid Parkinson's disease were treated successfully with adjunctive ziprasidone at doses of 80 to 160mg/d. Two of the patients had major depressive disorder, recurrent, with psychotic features (*Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* [DSM-IV] DSM-IV 296.34) and two had bipolar disorder, not otherwise specified (DSM-IV 296.8) and presented with psychotic and manic features. In three of the four patients, prior treatment with olanzapine or risperidone or both had failed to adequately control psychotic or manic symptoms; in some cases, the treatment worsened the Parkinson's symptoms.

Results: In all four patients, ziprasidone greatly improved psychosis and mood disturbances within days. All of the patients were also treated with other medications for comorbidities; these included one or more antiparkinsonian drugs, antidepressants, and, in one case, quetiapine for insomnia. There were no observed serious adverse events, extrapyramidal side effects, or worsening of movement disorder symptoms with the administration of ziprasidone in these patients. All patients remained stable on ziprasidone combination therapy for as long as they were followed, which ranged from several months to three years.

Conclusion: These results indicate that ziprasidone may be an efficacious and well tolerated therapy in patients with comorbid Parkinson's disease and psychiatric illness.



ADDRESS CORRESPONDENCE TO: Alan Berkowitz, MD, 11770 Bernardo Plaza Court, Suite 370, San Diego, CA 92128 Phone: (858) 673-1798/3360; Fax: (858) 592-0884; E-mail: alanberkowitz@msn.com

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Key Words: ziprasidone, elderly, Parkinson's disease, mood disorders

INTRODUCTION

The coexistence of movement disorders, including Parkinson's disease, in elderly patients with a history of mood disorder presents a unique challenge to the treating physician. Dopaminergic treatment for Parkinson's disease may be associated with adverse psychiatric effects, such as hallucinations and delusions,[1] while antipsychotic agents may have a negative effect on movement disorders. Conventional antipsychotic medications, as well as some atypical antipsychotics, are often not tolerated by patients with movement disorders.[1,2] The fact that elderly patients commonly have multiple comorbidities requiring treatment with numerous medications complicates their psychiatric management.

The risk of extrapyramidal side effects is generally lower with atypical antipsychotic agents than with conventional neuroleptics.[3] However, extrapyramidal effects aside, there are other important differences in safety and tolerability distinguishing the atypical antipsychotic drugs. Weight gain, diabetes, and worsening lipid profiles, for example, are associated with clozapine and olanzapine use.[4] Risperidone and quetiapine also tend to induce moderate weight gain, whereas aripiprazole and ziprasidone cause little or no weight increase.[4] Because the incidence of movement disorder symptoms with clozapine and quetiapine is relatively low, these drugs have been recommended for use in patients with Parkinson's disease who require treatment of psychotic symptoms.[5–9] However, the studies supporting such use have only investigated the treatment of psychosis induced specifically by antiparkinsonian drug therapy.[5–8] These agents were not studied systematically in patients with severe comorbid psychiatric disorders and Parkinson's disease.

The following case reviews describe the treatment of four elderly patients who had multiple comorbidities, including histories of mood disorders, and some level of movement disorder. All four were treated with ziprasidone for mood disorders with psychotic episodes in the hospital at the Behavioral Medicine Center and afterward in my office or an extended-care facility.

CASE 1

This male patient was an 86-year-old, divorced, former police officer with a history of major depressive disorder, recurrent, with psychotic features (*Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* [DSM-IV] 296.34). In addition to Parkinson's disease, he also had the following comorbidities: Hypertension, benign prostatic hypertrophy, elevated cholesterol, congestive heart failure, atrial fibrillation, and osteoarthritis.

Upon presentation to the Behavioral Medicine Center, he was clinically depressed and paranoid, exhibiting hostile behavior toward his assisted living staff. He was nonadherent to his medications and denied having Parkinson's disease, despite diagnosis by his internist, a neurologist, and myself. His symptoms of marked bradykinesia, rigidity, masked facies, dysarthria, and increased muscle tone were consistent with the diagnosis. His cognitive ability was not affected: He scored 29/30 on a Mini-Mental Status Examination (MMSE), drew a normal clock face, and had a normal word-finding assessment. Magnetic resonance imaging (MRI) of his brain indicated decreased basal ganglia volume, consistent with Parkinson's disease.

Upon admission (first of two hospital stays), he received a combination of sertraline 100mg/d and olanzapine up to 10mg/d. Although not confused, he demanded donepezil to prevent cognitive loss. This combination afforded only marginal improvement in his psychosis. Olanzapine was discontinued after 10 days and ziprasidone was initiated at 20mg b.i.d., then titrated to 40mg b.i.d. at meals. Within eight days, the psychosis resolved. After discharge, the patient complained of insomnia, for which he was administered quetiapine, titrated to 200mg/d. This successfully resolved the insomnia without any reported side effects. He had no deterioration of motor function, and though the dysarthria improved, it did not resolve.

At readmittance three months later, when he once again became nonadherent to the medication regimen, he had experienced recurrence of major depressive disorder with psychotic features (DSM-IV 296.34). He had stopped taking sertraline, carbidopa/levodopa, ziprasidone, and quetiapine. He was also bradykinetic, dysphagic, and dysarthric and had markedly increased muscle tone. Following a probable-cause hearing, required because he refused medications that he felt were poisoning him, he was treated with several intramuscular injections of ziprasidone 20mg. After seven days, his symptoms had cleared and he was consistently taking his medications (sertraline 100mg/d, carbidopa/levodopa 25 to 100mg t.i.d., ziprasidone 40mg b.i.d., and quetiapine up to 400mg for insomnia). The quetiapine dose was adjusted over three weeks. As with the first admission, there was no deterioration of motor function.

Over the next several months, the patient remained adherent to his medications and was event free. Thereafter, he moved his residence to be closer to his family and was lost to further follow-up.

CASE 2

This was an 85-year-old married woman with a 50-year history of bipolar disorder, not otherwise specified (NOS; DSM-IV 296.8). In addition to Parkinson's disease, she also had hypertension.

Despite adherence to her medications, she became manic, experiencing rapid speech and tangential, racing thoughts, together with paranoid ideation. She had insomnia and was irritable. She was too manic to fully cooperate with cognitive evaluation. Her medications included valproate sodium 1500mg/d (blood level=73µg/mL), carbidopa/levodopa 25 to 100mg t.i.d., and selegiline hydrochloride 5mg t.i.d. Olanzapine 20mg/d failed to control mania but did not aggravate the Parkinson's disease symptoms. Risperidone 2.5mg/d also failed to control her psychotic symptoms and greatly worsened her Parkinson's disease, causing increasing muscle rigidity, bradykinesia, tremors, and orthostatic hypotension. Reducing risperidone to 1mg/d did not improve motor function.

Upon the patient's admission to the Behavioral Medicine Center, risperidone was discontinued. Ziprasidone was initiated and titrated to 80mg b.i.d. with meals over the following eight days. Upon discharge 13 days after admission, the patient's mania had completely resolved, she scored 30/30 on the MMSE, and drew a clock face correctly. Moreover, there was improvement in her motor function: Decreased tremor and dysarthria, resolution of orthostatic hypertension, and marked improvement in the bradykinesia. She continues to do well three years post-discharge.

CASE 3

This 73-year-old woman from an assisted living residence had a 30-year history of bipolar disorder, not otherwise specified (DSM-IV 296.8). She also had Parkinson's disease and moderate dementia (DSM-IV 294.1), in addition to hypertension, congestive heart failure, and chronic obstructive pulmonary disease. She had undergone surgery for colorectal cancer.

The patient demonstrated symptoms of mania, including irritability, tangential thinking, and rapid speech. She was paranoid, refusing help with daily living activities, and accusing multiple long-term care givers of raping her. Prior to admission, she had been treated with risperidone 3mg/d, which failed to provide a clinical response and worsened her bradykinesia, muscle rigidity, orthostatic hypertension, and mild tremors. She began to fall. Risperidone was discontinued, and olanzapine was initiated and titrated to 20mg/d. Although this did not improve the mania, it did not worsen motor function.

Upon admission to the Behavioral Medicine Center, she showed cognitive impairment, scored 17/30 points on a MMSE, and refused a clock-face examination. An MRI scan of her brain was uninformative. Her medications included valproate sodium 1000mg/d (blood level=84 µg/mL), topiramate 50mg/d, olanzapine 20mg/d, and pramipexole 125µg t.i.d. The topiramate and olanzapine were discontinued; over the first four days, ziprasidone was titrated to 80mg b.i.d. with meals. Within seven days, the patient experienced complete resolution of mania and psychosis without deterioration of her motor function.

For 23 months, she remained on the same dose of ziprasidone without any resumption of psychiatric illness. At 23 months post-discharge, she died from relapsed colorectal cancer.

CASE 4

This was a 66-year-old woman who had been diagnosed with major depressive disorder, recurrent, with psychotic features (DSM-IV 296.34). Her comorbidities included Parkinson's disease, type 2 diabetes mellitus, breast cancer (past history), exogenous obesity, and two transient ischemic attacks. She was taking carbidopa/levodopa 25/100mg b.i.d. under the care of a neurologist as an outpatient.

Upon admission to the Behavioral Medicine Center, she complained of frequent crying episodes without clear reason, poor appetite, and feeling that she was a burden to her family. She also complained of auditory hallucinations that included scary, depressing music, which was particularly distracting and distressing. The MRI scan of her brain did not demonstrate basal ganglia volume loss or any other finding.

> The clinical response [to ziprasidone in all four cases] was sustained over several months with no observable dystonia or extrapyramidal side effects.

She was placed on venlafaxine (extended-release formulation), titrated to 150mg/d over 14 days. The hallucinations intensified, so the venlafaxine was rapidly tapered and discontinued. During the six days she remained off psychotropic medication, the hallucinations returned to their original level. Ziprasidone, titrated to 60mg b.i.d. with meals over three days, and sertraline, titrated to 100mg/d over five days, were initiated. The patient was subsequently released, 25 days after admission, with marked resolution of depression and complete resolution of psychosis.

In addition to providing rapid, effective treatment for psychosis, ziprasidone may have contributed to stabilizing mood disturbances, without exacerbating Parkinson's disease symptoms.

During the remaining six months that she was followed, the patient remained euthymic and without exacerbation of her Parkinson's disease.

DISCUSSION

All four of these patients suffered from mood disorders with psychotic features and had Parkinson's disease. All four patients demonstrated an excellent clinical response to treatment with ziprasidone at doses ranging from 40 to 80mg b.i.d., administered with meals, as instructed by the prescribing information, to ensure maximum absorption.[10] The clinical response was sustained over several months with no observable dystonia or extrapyramidal side effects.

In none of the four cases did ziprasidone cause significant side effects even though it was administered in combination with other drugs. The coadministered drugs included medications for movement disorders, valproate sodium or antidepressants, and in one case, quetiapine plus an antidepressant. Two patients came to the hospital on selegiline or pramipexole prescribed by either their primary doctor or by their neurologist. None of the patients had to discontinue ziprasidone therapy because of adverse events. Moreover, the effectiveness of ziprasidone was not affected by dose adjustments based on age or moderate degrees of hepatic or renal impairment.

Patients receiving dopaminergic treatment for movement disorders such as Parkinson's disease may exhibit hallucinations and delusions as side effects. Thus, it is unclear whether the mood disturbance and psychosis in the patients reviewed here were solely attributable to their preexisting mood disorders or were induced or exacerbated by pharmacotherapy for Parkinson's disease. Regardless of this etiologic uncertainty, it is always best, when treating mood disorders in patients with Parkinson's disease, to use medications that do not worsen the movement disorder symptoms. In two of the patients discussed here, risperidone exacerbated Parkinson's disease symptoms. Olanzapine did not affect the movement disorder, but neither did it effectively treat the psychosis. Ziprasidone, on the other hand, was effective and produced no observed effects on movement. This is consistent with the literature on ziprasidone, documenting its successful use in treating elderly patients with Parkinson's disease and psychosis, similar to the patients described here.[1,11–13]

The side effect profile of antipsychotics may be explained by their binding affinities at several neurotransmitter receptor sites. The difference between atypical and conventional antipsychotics generally derives from the fact that while atypicals antagonize both serotonin-2A (5-HT_{2A}) and dopamine D_2 receptors, conventionals antagonize only D_2 receptors.[14,15] Antagonism of mesolimbic D_2 receptors is thought to be important for controlling psychotic symptoms while 5-HT_{2A} receptor blockade counteracts the deleterious motor effects of dopamine receptor blockade in the striatum.[14] Among atypical antipsychotic agents, ziprasidone has the highest *in-vitro* 5-HT_{2A}/D_2 receptor affinity ratio, which may account for its association with a low incidence of extrapyramidal side effects.[14,16] Ziprasidone also has a low affinity for histamine H_1 and muscarinic M_1 receptors, thus largely avoiding side effects attributable to antagonism at these sites, such as weight gain (H_1) and cognitive dysfunction (M_1).[14]

Ziprasidone also exhibits high affinity for 5-HT_{1A} and 5-HT_{1D} receptors as well as moderate affinity for 5-HT and norepinephrine transporters, sites thought to play a role in

ameliorating symptoms of depression and anxiety.[14] In two of the presented cases, the patients were experiencing depression. Although these patients were also treated with sertraline, ziprasidone may have contributed to improving their depression.

Among our case studies, the woman affected by dementia in addition to psychosis (Case 3) responded to ziprasidone with complete resolution of her hallucinations within days. This response is consistent with the experience of Cole and colleagues,[17] who reported on four patients with dementia complicated by psychosis who also improved with ziprasidone treatment, without observed side effects.[17]

The cases presented here, along with the recent literature, demonstrate the effectiveness of ziprasidone in the treatment of acutely psychotic elderly patients with comorbid bipolar disorder or major depressive disorder and Parkinson's disease. In addition to providing rapid, effective treatment for psychosis, ziprasidone may have contributed to stabilizing mood disturbances, without exacerbating Parkinson's disease symptoms. Controlled clinical trials are necessary to confirm these encouraging findings.

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